## REMARKS

Claims 101-106, 109-116 and 119-128 were pending in the present application.

## THE DOUBLE PATENTING REJECTION

The double patenting rejection of the claims is maintained from the previous Office Action.

As requested previously, Applicants hereby request that the double-patenting rejection continue to be held in abeyance until the present claims are indicated to be allowable but for the double-patenting rejection, at which time Applicants intend to submit a Terminal Disclaimer, thereby obviating the rejection.

## REJECTION UNDER 35 U.S.C. § 103

The Examiner rejected claims 101-106, 109-116, and 120-128 under 35 U.S.C. 103 as being obvious over Abe *et al* in view of Oldham *et al* and further in view of Sahagan *et al*. Applicants respectfully traverse this rejection.

The Applicants respectfully direct the Examiner's attention to MPEP paragraph 707.07(j)(III) on "State When Claims are Allowable" and MPEP paragraph 707.07(g) on "Piecemeal Examination."

The Applicants respectfully assert that the Examiner has previously indicated that claim 101 is allowable. MPEP 707.07(II) recites that "[i]f a claim is otherwise allowable but is dependent on a canceled claim or on a rejected claim, the Office action should state that the claim would be allowable if rewritten in independent form." The Examiner recited in the Office Action of December 31, 2003 that claim 119 would be allowable if rewritten in independent form including all of the limitations of the base claim (*i.e.*, claim 101) and intervening claims (none). Without agreeing with the Examiner in any way, and merely to expedite prosecution, claim 101 was amended to recite that the "antibody comprises a human Fc region." Thus, independent claim 101, as amended, as well as the claims dependent therefrom, include the language of claim 119 that the Examiner indicated would make the claim allowable. Therefore, Applicants respectfully assert that claim 101 and any claims dependant therefrom are allowable.

Further, the Applicants respectfully assert that the Examiner should have applied any references to the dependant claims, if applicable, in the previous Office Actions.



PAGE 6/29 * RCVD AT 11/19/2004 5:01:00 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-1/1 * DNIS:8729306 * CSID:4255274109 * DURATION (mm-ss):12-30

MPEP 707.07(g) states "[p]iecemeal examination should be avoided as much as possible. The examiner ordinarily should reject each claim on all valid grounds available, avoiding, however, undue multiplication of references." In contrast to the guidance provided in MPEP 707.07(g), the Examiner should have applied any references to dependant claim 119 in the previous office actions, rather than indicate it contained allowable subject matter.

Further, the Applicants respectfully assert that the Examiner has not established a *prima facie* case of obviousness. As discussed in MPEP 2143,

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

**1. There is no suggestion or motivation to modify or combine Abe *et al* in view of Oldham *et al* and further in view of Sahagan *et al***

There is no suggestion or motivation, either in Abe *et al* in view of Oldham *et al* and further in view of Sahagan *et al* or in the knowledge generally available to one of ordinary skill in the art, to modify or combine the references. Abe *et al* fail to teach or suggest, as recited in claim 101, "[a]n immunoconjugate that comprises an antibody joined to a therapeutic agent...". The Examiner admits that "Abe *et al* do not specifically characterize the antibody as being in the form of an immunoconjugate." (Office Action of August 25, 2004, page 3, lines 18-19).

Further, there is no motivation in Abe *et al* that would suggest, as recited in claim 101, "an immunoconjugate that comprises an antibody joined to a therapeutic agent...". Abe *et al* can fairly be thought to disclose that the "AH6 antibody *may have prognostic value* for colonic polyps." (emphasis added) (Abe, pg 2643, right column (line 46-47)). Abe *et al* disclose that the plasma level of certain tumor associated antigens may have diagnostic value. (Abe, pg 2639, Abstract (lines 29-34) and pg 2639, right hand column



PAGE 7/29 * RCVD AT 11/19/2004 5:01:00 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-1/1 * DNIS:8729306 * CSID:4255274109 * DURATION (mm-ss):12-30

(lines 1-3)). Abe *et al* disclose the use of AH6 antibody to the tumor associated antigen for diagnostic and not therapeutic purposes.

Oldham *et al* fail to satisfy the deficiencies of Abe *et al*. The Examiner recites that "it was well known in the art at the time the invention was made that the conjugation of drugs or cytotoxic moieties to an antibody was well established in view of Oldham." Oldham *et al* briefly discuss the results of an *in vivo* study in guinea pigs using an immunoconjugate consisting of diphtheria toxin A-chain conjugated to the murine D3 monoclonal antibody. Oldham *et al* report that "after the initial therapeutic effect, the treated animals did *manifest tumor growth* and subsequently *died from progressive tumor growth*." (emphasis added) Oldham *et al*, Page 20, lines 19-22. Further, Oldham *et al* recite that techniques to conjugate an antibody to a variety of toxic substances are difficult and require further refinement. Oldham *et al*, page 22, lines 25-27. Oldham *et al* lists as one prerequisite of toxic conjugates to be effective "internalization, perhaps through antigenic modulation, must occur." Oldham *et al*, page 22, lines 30-32.

Sahagan *et al* do not satisfy the deficiencies of either Oldham *et al* or Abe *et al*. Sahagan *et al* do not even discuss immunoconjugates, let alone their therapeutic use.

**2. There is no reasonable expectation of success in the combination of Abe *et al* in view of Oldham *et al* and further in view of Sahagan *et al***

There is no reasonable expectation of success in the combination of Abe *et al* in view of Oldham *et al* and further in view of Sahagan *et al*. The Examiner recites that "one of skill in the art would have been motivated to couple the AH6 antibody to a therapeutic agent to form an immunoconjugate wherein the antigen binding domains target drugs or cytotoxic agents to carcinomas, because Abe *et al* taught the effectiveness and targeting ability of the AH6 antibody for carcinoma." The Applicants must respectfully disagree that one of skill in the art would not have been motivated by the disclosure of Abe *et al* to couple the AH6 antibody to a therapeutic agent to form an immunoconjugate.

The disclosure of Abe *et al* actually *teaches away* from a therapeutic immunoconjugate. As stated in MPEP 2145(X)(D)(2), "[i]t is improper to combine



PAGE 8/29 * RCVD AT 11/19/2004 5:01:00 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-1/1 * DNIS:8729306 * CSID:4255274109 * DURATION (mm-ss):12-30

references where the references teach away from their combination." A reference may be said to teach away when a person of ordinary skill, upon reading it, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path taken by the inventor. (Monarch Knitting Mach. Corp. v. Sulzer Morat Gmbh, 139 F.3d 877, 45 USPQ 2d 1977 (Fed. Cir. 1998); Para-Ordnance Mfg. v. SGS Importers Int'l, Inc., 73 F.3d 1085, 37 USPQ2d 1237 (Fed. Cir. 1995); In re Gurley, 27 F.3d 551, 31 USPQ2d 1130 (Fed. Cir. 1994).) In general, a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the inventor. (In re Gurley, 27 F.3d 551, 31 USPQ2d 1130 (Fed. Cir. 1994)). Abe *et al* disclose that certain tumor associated antigens in human gastrointestinal tumors may be released into the plasma of patients with cancer, and the levels of these antigens have been found to be of diagnostic value. (Abe, pg 2639, Abstract (lines 29-34) and pg 2639, right hand column (lines 1-3)). To one of skill in the art, a reference which discloses the shedding of a tumor associated antigen would teach away from its targeting with an immunoconjugate. It is not desirable to construct a therapeutic immunoconjugate to a tumor associated antigen which is shed into the plasma because the antigen is not localized to the tumor. Therefore, an immunoconjugate could bind to the systemically shed antigen and lead to non-localized, systemic release of the toxic agent.

Certain problems still present themselves in the development of an immunoconjugate. In vitro, the activity of immunoconjugates is affected by the number of target antigens on the cell surface, the internalization of the immunoconjugates, the kind of toxin, the class of the antibody, the kind of linkage, and by other factors. Dillman, *Annals of Internal Medicine* 111:592-603,595,596 *(1989)*.[1] Several problems arise with in vivo administration of immunoconjugates. The short serum half-life of immunoconjugates, due to their rapid hepatic uptake, decreases the number of immunoconjugate molecules that reach a solid tumor. This, together with low tumor penetration by immunoconjugates, could lead to low anti-tumor activity. Heterogeneity of tumors, immunogenicity of immunoconjugates, sometimes marked differences in the biodistribution of antibody-drug conjugates from those seen with free antibody, the



PAGE 9/29 * RCVD AT 11/19/2004 5:01:00 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-1/1 * DNIS:8729306 * CSID:4255274109 * DURATION (mm-ss):12-30

shedding of tumor antigens into the circulation, and cross-reactivity of immunoconjugates with normal tissues are other factors that might limit the clinical use of immunoconjugates. Further, in order for an immunoconjugate to be effective, the antibody with the immunoconjugate must be internalized and the cytostatic or cytotoxic component of the immunoconjugate cleaved and released in an active form within the cell. Dillman, pg 595, 596. For example, not all antigens are presented in a non-steriohindered manner and/or are internalized. Further, not all drugs will be cleaved from the antibody if the immunoconjugate is internalized to release an active form of the drug. Dillman, 595, 596. Therefore, it cannot be presumed that any immunoconjugate will have a reasonable expectation of success.

The Applicants respectfully assert that since Abe *et al* teaches away from "[a]n immunoconjugate that comprises an antibody joined to a therapeutic agent" as claimed in claim 101, it should not properly be combined with Oldham *et al* and Sahagan *et al*. MPEP 2145(X)(D)(2). However, even if it were, Oldham *et al* do not satisfy the deficiencies of Abe *et al*. As recited above, Oldham *et al* discuss an experiment using an immunoconjugate that resulted in tumor growth and subsequently death of the test animals from progressive tumor growth. Oldham et al, Page 20, lines 19-22. Oldham *et al* is not indicative of a "reasonable expectation of success" of an immunoconjugate.

Also as mentioned above, Sahagan *et al* do not satisfy the deficiencies of either Oldham *et al* or Abe *et al*. Sahagan *et al* do not even discuss immunoconjugates, let alone their therapeutic use.

The Examiner recites that Sahagan *et al* teach the construction of a chimeric antibody comprising a mouse variable region and a human constant region, wherein the purpose of such a construction is to reduce the side effects associated with mouse constant regions in eliciting an unwanted immune response. However, Applicants respectfully assert that the addition of a human Fc region onto a mouse antibody may not circumvent the immune response. For example, Baert *et al* N Engl J. Med 348 (7):601-8 (2003) (attached hereto as Exhibit A) describe treatment with infliximab, a chimeric monoclonal IgG1 antibody against tumor necrosis factor, resulted in the formation of

[1] Cited by Applicants as DD In Information Disclosure Statement dated August 9, 2000.



PAGE 10/29 * RCVD AT 11/19/2004 5:01:00 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-1/1 * DNIS:8729306 * CSID:4255274109 * DURATION (mm-ss):12-30

antibodies against infliximab in 61% of patients. Baert et al concluded that the development of antibodies against infliximab is associated with an increased risk of infusion reactions and a reduced duration of response to treatment. Further, Welt *et al* Clin Cancer Res 9:1338-1346 (2003) (attached hereto as Exhibit B) describe studies conducted with mAb A33, a murine IgG2a that has been humanized, including the addition of a human Fc region. The results of a Phase I clinical trial showed eight of 11 patients developed a HAHA response. Significant toxicity was limited to four patients who developed high HAHA titers. In two of these cases, infusion-related reactions such as fevers, rigors, facial flushing, and changes in blood pressure were observed, whereas in the other two cases, toxicity consisted of skin rash, fever, or myalgia. Therefore, chimeric or humanized antibodies having an Fc portion may not "reduce the side effects associated with mouse constant regions in eliciting an unwanted immune response." The Applicants respectfully assert that it would not have been obvious to construct "[a]n immunoconjugate that comprises an antibody" wherein "the antibody comprises a human Fc region" as claimed in claim 101 and any claims dependant therefrom.

**3. The references do not teach or suggest all the elements of the claims**

Abe *et al* in view of Oldham *et al* and further in view of Sahagan *et al* fail to teach or suggest "an immunoconjugate that comprises an antibody joined to a therapeutic agent" as claimed in claim 101. Abe *et al* does not teach or suggest an immunoconjugate. To one of skill in the art, Abe *et* al actually teaches away from an immunoconjugate by discussing shedding of the tumor associated antigen. While mentioning immunoconjugates, Oldham *et al* disclose techniques to conjugate an antibody to a variety of toxic substances are difficult and require further refinement. Sahagan *et al* do not discuss immunoconjugates, let alone a therapeutic immunoconjugate. Therefore, the references do not teach or suggest, as recited in claim 101, "an immunoconjugate that comprises an antibody joined to a therapeutic agent." As such, claim 101 and any claims dependant therefrom, are unobvious over Abe *et al* in view of Oldham *et al* and further in view of Sahagan *et al.*

**CONCLUSION**

Applicants respectfully request that the amendments and remarks of the present response be entered and made of record in the instant application. Claims 101, 102, 104-



PAGE 11/29 * RCVD AT 11/19/2004 5:01:00 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-1/1 * DNIS:8729306 * CSID:4255274109 * DURATION (mm-ss):12-30

106, 109-116 and 120-127 fully meet all statutory requirements for patentability. Withdrawal of the Examiner's rejections and allowance and action for issuance are respectfully requested.

Applicant respectfully requests that the Examiner call the undersigned attorney at (425)527-4122 if any questions or issues remain.

Respectfully submitted,

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PAGE 12/29 * RCVD AT 11/19/2004 5:01:00 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-1/1 * DNIS:8729306 * CSID:4255274109 * DURATION (mm-ss):12-30